National Cancer Institute

Complex statistical approaches and uncertainties: modeling dose error

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Outline of talk

- Dose measurement error: why does it matter?
- How does measurement error arise in medical and occupational studies?
  - Shared *vs* unshared errors
  - Berkson *vs* classical error
- Regression calibration methods
- Full likelihood methods
  - Monte Carlo Maximum Likelihood
  - Bayesian Markov Chain Monte Carlo (MCMC)
- Bayesian MCMC and regression-calibration methods applied to latest Japanese A-bomb mortality data (UNSCEAR 2006 report)
- Conclusions

Dose measurement error: why does it matter?

- Dose measurement error is an inescapable part of the dose assessment process *via* reading of film badges, dose-rate meters etc
- Dose measurement error (particularly classical measurement errors, as we shall see), biases trends with dose towards null, leading to underestimation of radiation risk

Shared *vs* unshared errors

- Often assumed that errors in dose for each individual are independent (unshared error)
- In some situations there can be common component in errors in dose between individuals (shared error)
  - Errors in the yields of the Hiroshima or Nagasaki bombs, shielding factors
  - Errors in factors used to convert “recorded doses” to organ doses in nuclear worker studies

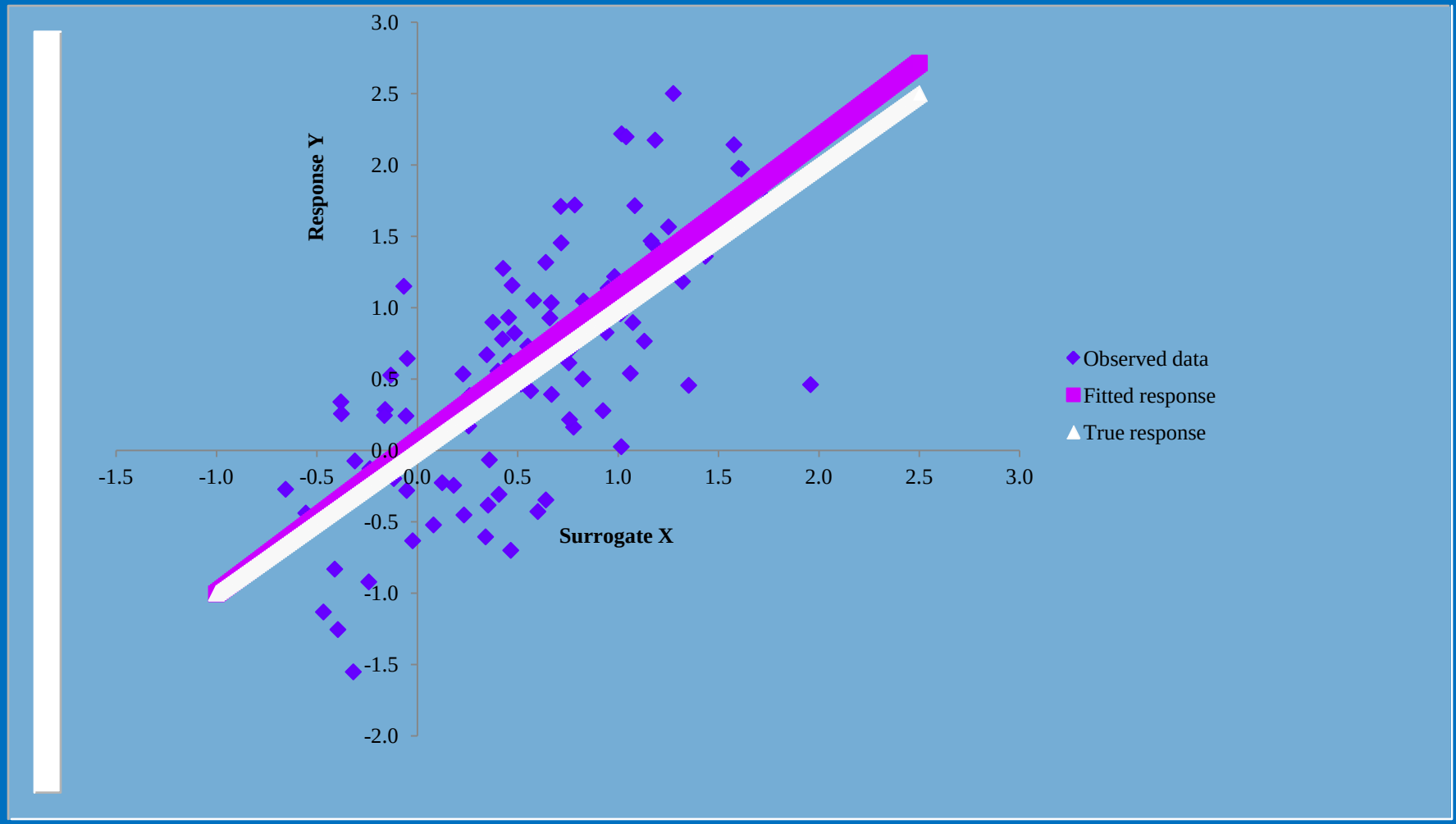
Impact of shared errors

- Simplest situation:
  - Error shared by all subjects
  - Expected value of the *estimated dose* = K x *true dose*
  - Estimates of linear risk coefficients biased by a factor K
  - Desirable to include uncertainty in K in confidence intervals
- More complex situations:
  - Expected value of the *estimated dose* depends in a complicated way on the *true dose* and several uncertainly estimated parameters
  - Various subsets of subjects share different errors

Berkson dose measurement error (grouping error)

- Error is independent of observed dose
- In epidemiology Berkson errors arise when average dose for group of subjects is used as dose estimate for all members of that group
- Variance of true doses larger than variance of measured doses
- Little distortion in linear dose-response

Berkson dose measurement error



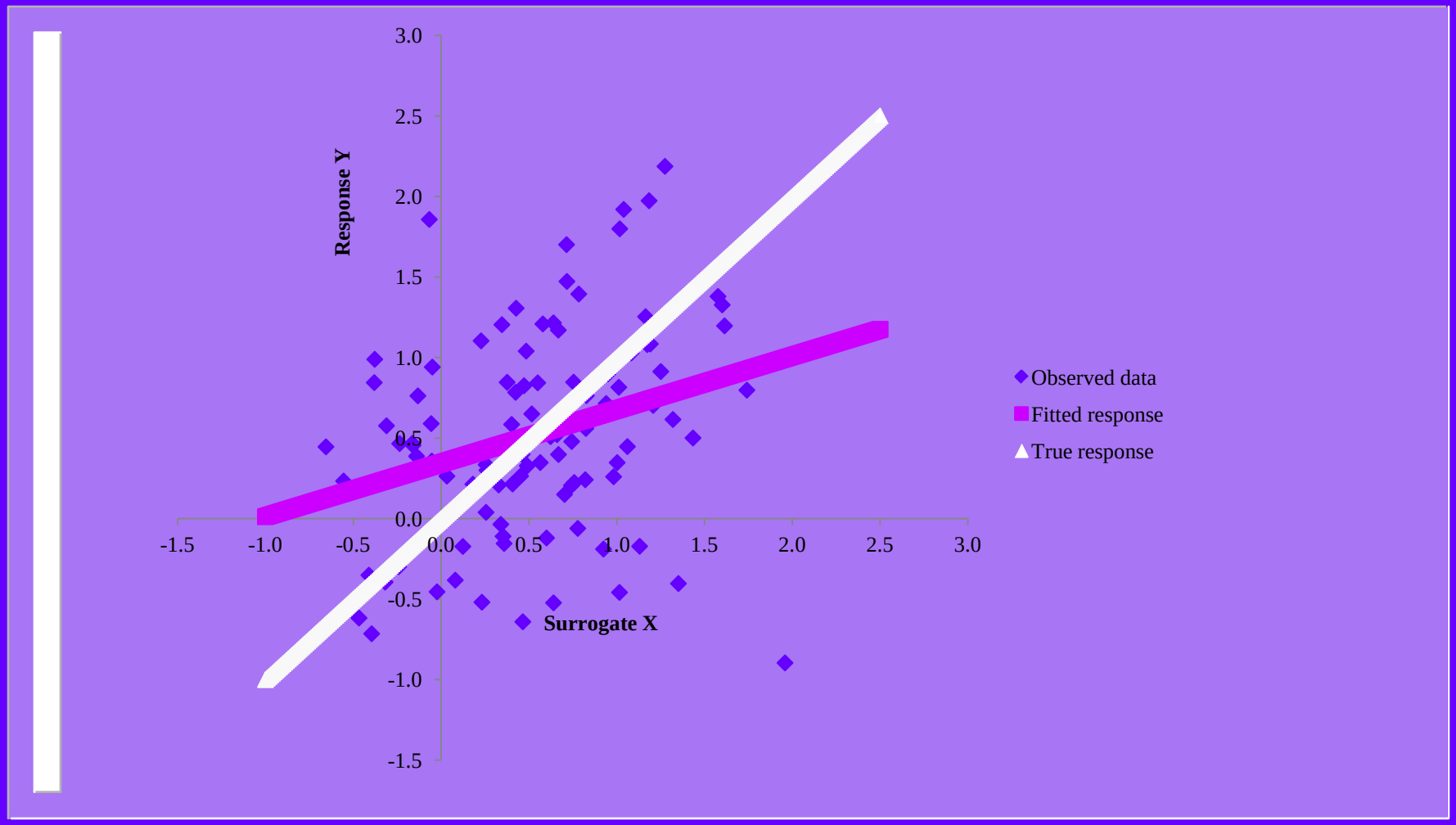
Example of Berkson measurement error

- In radiotherapy, radiation doses, W_i, are estimated with reference to the physical parameters of the machine (voltage of X-ray set, filtration etc): the actual dose received by the patient, X_i, will vary at random around this value, so that $W_i = E[X_i \mid W_i]$ (i.e., Berkson error model), although the distribution of true dose can be markedly skew.

Classical dose measurement error

- Error is independent of true dose
- Can be thought of as error that arises from an imprecise measuring device
- Variance of estimated doses larger than variance of true doses
- Adjustment needed to avoid attenuation of the true dose-response

Classical dose measurement error



Example of classical measurement error

- In Japanese atomic bomb survivors, radiation doses are estimated using estimates of position of survivors in each city, orientation with respect to bomb and other shielding structures, e.g., buildings. In this case estimated doses, W_i, thought to be lognormally distributed around true doses, X_i, so that $X_i = E[W_i | X_i]$ (i.e., classical error model)(Jablon TR 23-71 1971)

  NB: some aspects of A-bomb dosimetry (errors in source term, shielding) imply component of Berkson error, shared error (Pierce *et al Radiat Res* **170**:118-36;2008)

Regression calibration methods used to model measurement errors

- 1st order regression calibration (Carroll *et al. Measurement error in nonlinear models: a modern perspective*, Chapman & Hall 2006): relatively simple to apply
- Replace true dose X_i with its expectation with respect to observed dose

  $E[X_i | W_i]$ in all regression equations
- Only uses 1st order terms in Taylor expansion (Rosner *et al. Stat Med* **8**:1051-69;1989, Carroll *et al.* 2006): does not take account of full variability
- When dosimetric errors not too great, variability not taken into account modest

Advantages of regression calibration

- Relatively simple to implement: once plug-in estimates $E[X_i | W_i]$ are calculated, can substitute into normal statistical software
- At least when dose errors are modest the amount of variability not taken into account is relatively modest
- Provides unbiased estimates of risk for linear disease models and “almost” unbiased estimates for non-linear models
- In almost all cases provides good tests of the null hypothesis of no radiation effect, but upper confidence limits may be underestimated

Disadvantages of regression calibration

- Does not take full account of uncertainty distribution (unlike full-likelihood methods (Bayesian MCMC, Monte Carlo maximum likelihood)): this may matter when both dose errors are large and when risks are large
- Unlike Bayesian MCMC, models do not give feedback from disease model to dose estimates

Full-likelihood methods

- Full-likelihood methods use number of linked probability models
- Two main types
  - Bayesian Markov Chain Monte Carlo
  - Monte Carlo Maximum Likelihood
- As outlined by Clayton (*Stat Med* **7**:819-41;1988) must specify three linked models (components of likelihood)
  - **Disease model** linking disease, "true" dose and other variables
  - **Dose model** linking "true" dose to observed dose
  - **Exposure model** specifying true dose distribution (i.e. structural model) (not always needed)

Bayesian MCMC methods

- Fundamental to Bayesian approach is that model parameters (γ_k), missing data, treated as if random
- Need to specify prior distributions for parameters: most often choose vague (uninformative) priors

Complete likelihood

- Obtain complete likelihood by putting together these components

Likelihood = Prob[disease|true dose]

× Prob[observed dose|true dose]

× Prob[true dose]

Monte Carlo maximum likelihood

- Basic idea: integrate likelihood over unknown parameters (true dose, etc), to get marginal likelihood
- One can then perform inference (via maximum likelihood on unknown model parameters) in normal way
- In general integrations are analytically intractable
- The integrations are generally performed numerically, via random sampling (over true dose conditional on observed dose)

Bayesian methods: sampling from posterior density

- Bayes theorem:

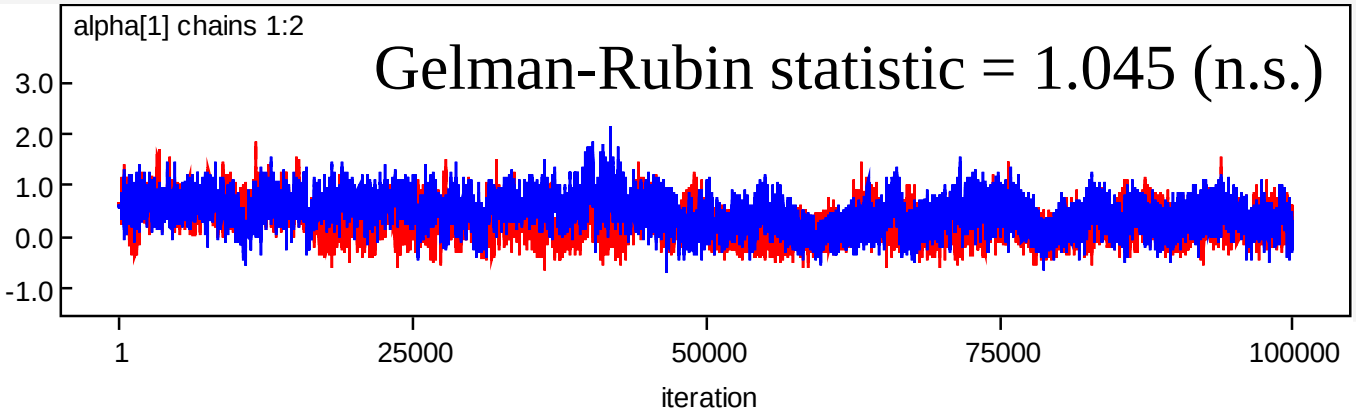
  Posterior density = C × Prior × Likelihood
- How to sample from posterior density?
- How to perform inference on this, e.g., many unknown parameters (some possibly nuisance), also unknown true doses? What about normalising constant C?
- One approach - integrate out unknown variables (as in Monte Carlo maximum likelihood – previous slide)
- Alternatively, use Markov Chain Monte Carlo (MCMC) methods: construct iterative sample of parameters that approximates to posterior distribution

Bayesian methods: Metropolis-Hastings sampling from posterior

- Metropolis-Hastings algorithm most flexible way of sampling from posterior density
- Iterative process guaranteed (subject to certain regularity conditions) to converge to posterior distribution

Bayesian methods: assessing convergence

- Although Metropolis-Hastings algorithm guaranteed to converge to posterior distribution: how to know convergence has happened?
- Use multiple long chains (different starting values) and compare within-chain to between-chain variance (Gelman-Rubin statistic)
- Arguably safer to compare mixing visually



Full likelihood (Monte Carlo ML, Bayesian MCMC) methods implementation

- Monte Carlo maximum likelihood generally requires code to be written in high level language (C++, Fortran)
- Bayesian error models easily specified in WinBUGS, JAGS (but both can be slow)
- These programs have facilities to check convergence via Gelman-Rubin plots, autocorrelation plots etc
- Easy to specify complex error models, e.g., combination of Berkson/classical errors, validation study
- Permits modular description of components of model via conditional independence relationships

Advantages of full likelihood methods (Monte Carlo ML, Bayesian MCMC)

- Takes full account of uncertainty distribution (unlike regression calibration)
- In Bayesian MCMC uncertainty easily propagated to risk (via sample from posterior distribution)(more on this later in relation to A-bomb data)
- In principle easily possible to specify complex models (particularly in Bayesian MCMC, via WinBUGS / JAGS) in modular way: very suitable for occupational and medical studies with complex dosimetry
- Unlike regression calibration, models give feedback from disease model to dose estimates

Disadvantages of full likelihood methods (Monte Carlo ML, Bayesian MCMC)

- Computational time
- For Bayesian MCMC convergence an issue: can be sure it has happened?
- Generally need to specify distribution of true dose (unknown)
- For Bayesian MCMC need to specify priors (though vague priors often used)
- Dependence on full probability model (unlike regression calibration): can be sure this is correct?

Application to Japanese A-bomb survivors (UNSCEAR 2006, Little *et al Radiat Res* **169**:660-76;2008)

- Members of Life Span Study interviewed or completed variety of questionnaires
- On basis of answers established survivor positions in two cities at time of bombings, orientation with respect to point of detonation of bomb, shielding by buildings and neighboring structures
- Using this information various sets of dose estimates to survivors calculated (T57D, T65DR, DS86, DS02)

Application to Japanese A-bomb survivors: errors in dose estimates

- Jablon (*ABCC TR 23-71*, 1971), Gilbert (*Radiat Res* **98**:591-605;1984) and Pierce *et al.* (*Radiat Res* **123**:275-84;1990) considered form of dose errors in A-bomb data
- Errors arise from number of sources
  - Uncertainties in source term, i.e., bomb yield
  - Uncertainties in radiation transport calculations
  - Uncertainties in shielding by buildings and other structures
  - Incorrect recall of position in cities by survivors
  - Incorrect recall of orientation with respect to bomb by survivors
- 10-20% of uncertainty contributed by survivor location, 10-15% by survivor orientation

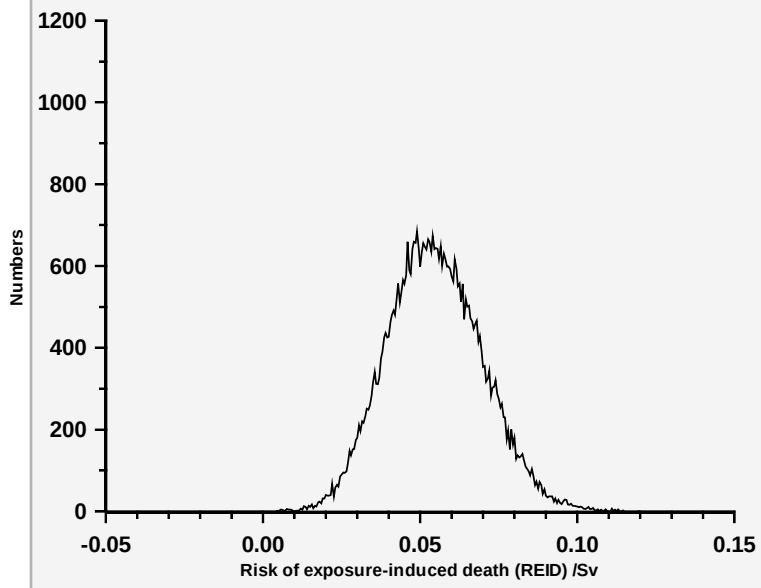
Application to Japanese A-bomb survivors: assumptions in dosimetric error modeling

- Applied to latest mortality DS02 data (Preston *et al.* *Radiat Res* **162**:377-89;2004)
- Classical dosimetric error model, log-normal errors – independent (unshared) errors
- 35% geometric standard deviations (GSD) errors
- Weibull distribution of "true" dose
- Vague priors
- Same assumptions used for regression calibration fit (comparison with Bayesian MCMC)
- These assumptions used by many others (Jablon *ABCC TR 23-71*, 1971, Pierce *et al. Radiat Res* **123**:275-84;1990)

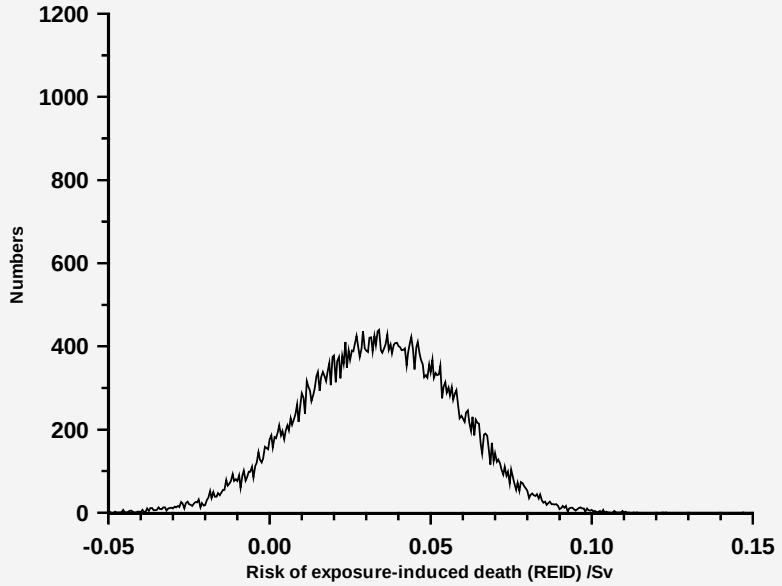
Solid cancer risk distribution for 2003 UK population, LQ *vs* LQE (ERR, test dose =0.1 Sv)

(UNSCEAR 2006, Little *et al Radiat Res* **169**:660-76;2008)

Linear-quadratic model



Linear-quadratic-exponential model



Linear-quadratic-exponential model more widely dispersed risks than linear-quadratic, substantial proportion of risk below 0

Cancer risks (all % per Sv, REID, current UK population) (UNSCEAR 2006, Little *et al Radiat Res* **169**:660-76;2008)

	Solid cancer	Leukemia
UNSCEAR 2000 (D=1.0 Sv, EAR, ERR, UK population)	7.9 – 14.4	0.95
BEIR VII (D=0.1 Sv, mixed ERR/EAR, US population)	7.95 – 9.8	0.33 – 0.79
Regression calibration (UNSCEAR 2006) (D=0.1 Sv, ERR, LQ, UK population)	5.26	0.42
Bayesian MCMC (UNSCEAR 2006) (D=0.1 Sv, ERR, LQ, UK population)	5.45 (90% CI 3.06 – 7.99)	0.50 (90% CI 0.11 – 0.97)

Bayesian MCMC and regression calibration estimates similar

Regression calibration (RC) *vs* Bayesian MCMC for A-bomb survivors

- Both likelihood-based methods
- 1st order RC simpler to implement, given grouped nature of A-bomb data
- 1st order RC less computationally intensive (minutes *vs* days)
- Differences between RC maximum-likelihood (mode) *vs* Bayesian MCMC (mean, median)
- Bayesian MCMC takes greater account of variability, and allows feedback disease model→doses, but when dosimetric errors and disease "signal" small, variability not taken into account by RC small

Conclusions

- Regression calibration methods are simple to implement and work well when magnitude of dose errors and risk are not large
- Full-likelihood (Monte Carlo maximum likelihood, Bayesian MCMC) methods potentially account for more uncertainty than regression calibration – but numerically intensive
- Full likelihood methods easily allows for complex dosimetry systems, as, e.g., found in many medical, occupational studies
- Bayesian MCMC methods not recommended for A-bomb survivor data (problems with grouped data)
- For A-bomb survivors regression calibration methods simpler, less computationally intensive, account for most of uncertainty